II. Support for the Amendment

Claim 38 has been amended to correct a typographical error.

Support for the amendment of claims 75 and 80-82 is found in the specification at page 3, line 2.

Support for new claims 87 and 88 is found in the specification at page 16, line 10 to page 17, line 16.

No new matter has been added.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider and withdraw all of the outstanding objections and rejections.

III. The Objection Under 37 C.F.R. 1.75(c) Must Be Withdrawn

At page 2 of the Office Action, the Examiner objects to claims 50-61 for "[B]eing in improper form because they are substantial duplicates of claims 25-36 . . . and also as being of improper dependent form because they ultimately depend from themselves." Applicants respectfully disagree.

Claims 50-61 are product-by-process claims. Since product-by-process claims are proper (*see* M.P.E.P. § 2173.05(p)), claims 50-61 are in a proper form, and are not duplicative of claims 25-36. Accordingly, Applicants respectfully request that this objection be withdrawn.

IV. The Obviousness-Type Double Patenting Rejection Must Be Withdrawn

At page 3 of the Office Action, the Examiner provisionally rejects claims 25-86 as allegedly obvious over claims 20-49 of copending Application No. 08/903,987. Applicants respectfully traverse this rejection. Application No. 08/903,987 has been abandoned, and a Notice

of Abandonment has been issued. Therefore, the alleged ground for this rejection is moot, and Applicants respectfully request that this objection be withdrawn.

V. The Rejection Under 35 U.S.C. § 112 Must Be Withdrawn

Claim 65 stands rejected as allegedly not enabled. Applicants respectfully traverse this rejection.

A. A Prima Facie Case of Non-Enablement Has Not Been Established

The examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, citing *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The examiner is obliged to accept the statements of the specification as being correct unless good reasons can be given for not doing so. *See* M.P.E.P. 2164.05, citing *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971). No good reasons have provided for not accepting that the statements of the specification are correct.

The test of enablement is whether undue experimentation would have been required to make and use the claimed invention. *See* M.P.E.P. § 2164.01, citing *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Thus, for a proffered basis for questioning enablement to be adequate, the proffered basis must support a conclusion that undue experimentation would have been required to make and use the claimed invention. Claim 65 is directed to a method for inducing a TH_1-type immune response in a mammal, comprising administering the composition of claim 25 to a mammal. No basis for supporting a conclusion that undue experimentation would have been required has been proffered.

The Examiner states:

> [T]specification, while being enabling for a TH1 response in mice, does not reasonably provide enablement for this response in any mammal, including a human. The specification . . . teaches a large increase in IgG2a in mice as indicative of stimulation of TH1 lymphocytes. The art teaches that TH1 lymphocytes are associated with generation of IgG2a antibodies in mice, but that the equivalent human subclasses are unknown (see Couper et al., . . . Human Immunology, 1998, V59, N8, pp. 493-499 1998). The specification does not enable any person skilled in the art to . . . practice the invention commensurate in scope with this claim.

The Examiner's stated ground for questioning the enablement of the claimed invention is insufficient to establish a *prima facie* case of non-enablement. The Examiner appears to have assumed, incorrectly, that claim 65 is directed to a method for "inducing the level of IgG2a" in a mammal. It is not. Claim 65 is directed to a method for "inducing a TH_1-type immune response" in a mammal comprising administering the vaccine composition of claim 25. In mice, a TH_1-type immune response can be exhibited by an increase in IgG2a levels. Even if a human equivalent of murine IgG2a has not been described, the invention is claim 65 is enabled.

Indeed, it is irrelevant whether a human equivalent of murine IgG2a exists. The issue is whether prior to November14, 1995,[1] one of ordinary skill in the art could have determined, without undue experimentation, if a human subject experienced a TH_1-type immune response after receiving the vaccine composition of claim 25. The answer is *yes*.

B. Only Routine Experimentation Would Have Been Required To Practice the Method of Claim 65

1. A TH_1-Type Immune Response Occurs In Humans

It is clear from the pre-filing date literature that one of ordinary skill in the art would have understood that a TH_1-type immune response occurs in humans. For example, Barnes, P.F. *et al.*,

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[1] The present application is the U.S. national phase of international application no. PCT/FR95/01495, filed November 14, 1995)

Infection and Immunity 61: 197-203 (1993) ("Barnes," provided herewith as attachment 1), teaches that in *Leishmania*-infected mice, TH_1 cells producing interferon-γ contribute to the control and elimination of infection, and that TH_2 cells producing interleukin-4 result in progressive and uncontrolled disease. *See* Barnes at page 197, first paragraph. Barnes further teaches that human T-cell subpopulations defined by cytokine patterns analogous to murine TH_1 and TH_2 cells are thought to play a central role in infectious diseases and allergic disorders. *See* Barnes at page 200, second full paragraph.

Romagnini, S., *J. Clin. Immunology 15*: 121-129 (1995) ("Romagnani," provided herewith as attachment 2), teaches that TH_1 cells occur functionally *in vivo* in humans. *See* Romagnini at page 123, first paragraph.

Katsikis, P.D. *et al.*, *Intl. Immunology 7*: 1287-1294 (1995) ("Katsikis," provided herewith as attachment 3) teaches that human $CD4^+$ T cells have, like their murine counterparts, have been classified on the basis of their cytokine profile, and that TH_1 cells produce interleukin-2 and interferon-γ. *See* Katsikis at the abstract.

Del Pret, G. and S. Romagnani, *Trends in Microbiology 2*: 4-6 (1994) ("Del Pret," provided herewith as attachment 4), teaches that human $CD4^+$ T cell clones with functional properties similar to those of murine TH_1 and TH_2 cells have been derived from the peripheral blood and other fluids of normal and ill humans. *See* Del Pret at page 4, last paragraph. Del Pret also teaches that viral infections usually result in activation of T cells that secrete TH_1-type cytokines. *See* Del Prete at page 5, middle column, last full paragraph. Del Prete also teaches that T cell clones specific for influenza virus, derived from normal human subjects vaccinated with influenza virus, showed a TH_1 profile. *See* Del Prete at page 5, middle column, last paragraph.

Thus, prior to the filing date of the present application, one of ordinary skill in the art would have understood that TH_1-type immune response occurs in humans.

2. A TH_1-Type Immune Response Could Have Been Detected Without Undue Experimentation

The pre-filing date literature also teaches how a TH_1-type immune response could have been assayed in a human subject. As discussed above, TH_1-type cells secrete interferon-γ. Ghalib, H.W. *et al.*, *J. Immunology 154*: 4623-4629 (1995) ("Ghalib," provided as attachment 5) teaches that a TH_1-type response can be assayed by culturing peripheral blood mononuclear cells and assaying for interferon-γ secretion. *See* Ghalib at page 4624.

Sieling, P.A. and R.L. Modlin, *Immunobiology 191*: 378-387 (1994) ("Sieling," provided herewith as attachment 6) teaches that TH_1-type cells secrete interleukin-2 and interferon-γ. Sieling also teaches a method for assaying secretion of those cytokines by T-cells. In the method taught by Sieling, RNA was extracted from leprosy lesions, cDNA was synthesized, and the polymerase chain reaction (PCR) was used to measure cytokine mRNA levels.[2] *See* Sieling at page 379. As shown in Figure 2 (page 380), a TH_1-type cytokine pattern was detected.

Thus, prior to the filing date of the present application, one of ordinary skill in the art would have been able to assay for a TH_1-type immune response without undue experimentation.

C. Summary

The method of claim 65 could have been practiced without undue experimentation. *No* reasons as to why undue experimentation would purportedly have been required to make and use the claimed invention have been provided. Therefore, a *prima facie* case of non-enablement has

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[2] Although Sieling used leprosy lesions as the source of RNA, *any* tissue or type of cell could have been used to practice the claimed invention, because prior to November, 1995, the reverse transcription-PCR technique was readily available to those of ordinary skill in the art were

not been established. This rejection is improper, and Applicants respectfully request that this rejection be reconsidered and withdrawn.

VI. The Rejections Under 35 U.S.C. § 103 Must Be Withdrawn

Claims 25-86 stand rejected as allegedly obvious over Bolcsak *et al*, U.S. Patent No. 5,100,662 ("Bolcsak") in view of Gao *et al.*, *Biochem. Biophys. Res. Comm. 179*: 280 (1991) ("Gao"); and separately over (2) Popescu *et al.*, EP 356,339 ("Popescu") in view of Epand *et al.*, U.S. Patent No. 5,283,185 ("Epand"). Applicants respectfully traverse these rejections.

A. Bolcsak and Gao Fail To Establish A Prima Facie Case of Obviousness

1. Bolcsak and Gao Each Fail To Suggest the Claimed Invention

a. Bolcsak Fails to Teach a Carbamoyl Linkage, the Claimed Compounds, or the Claimed Methods

Claims 25-37 are directed to a vaccine composition comprising at least one antigen and at least one amphipathic compound possessing a lipophilic group derived from a sterol linked to a cationic group via a carbamoyl group.

Bolcsak provides liposomes and vesicles formed from derivatized sterols. To the extent that Bolcsak teaches a structure that requires a chemical bridge (*see* component (B) in Figure 1 of Bolcsak, at c. 5), Bolcsak fails to suggest that the chemical bridge should be a carbamoyl group. Indeed, the Examiner admits that Bolcsak fails to suggest a carbamoyl group (Office Action at 5). Thus, Bolcsak fails to suggest the invention of claims 25-37.

Claims 30-32 recites specific amphipathic compounds. Because Bolcsak fails to suggest any of the recited compounds, Bolcsak fails to suggest the invention of claims 30-32.

Claim 35 requires that the vaccine composition also contain one of two specific neutral lipids. Because Bolcsak fails to suggest a composition containing both an amphipathic compound (with a carbamoyl linkage) and a neutral lipid, Bolcsak fails to suggest the invention of claim 35.

Claims 38-49 are directed to a method of making the vaccine composition of claim 25. For the same reasons that Bolcsak fails to suggest the invention of claims 25, Bolcsak fails to suggest the invention of claims 38-49.

Claims 50-61 are directed to the vaccine composition obtained by the method of claim 38, which in turn depends from claim 25. For the same reasons that Bolcsak fails to suggest the vaccine composition of claim 25, Bolcsak fails to suggest the vaccine composition of claims 50-61.

Claims 62-73 are directed to methods for inducing an immune response comprising administering the vaccine composition of claim 25 to a mammal. For the same reasons that Bolcsak fails to suggest the invention of claims 25, Bolcsak fails to suggest the invention of claims 62-73. Moreover, since Bolcsak fails to suggest a method of specifically inducing a cytotoxic T cell response or a TH_1-type immune response, Bolcsak fails to suggest the methods of claims 64 and 65.

Claim 74 is directed to a product comprising at least one antigen and one amphipathic compound possessing a lipophilic group derived from a sterol linked to a cationic group via a carbamoyl group. Because Bolcsak fails to suggest a carbamoyl linkage, Bolcsak fails to suggest the invention of claim 74.

Claims 75-86 are directed to a method for inducing an immune response in a mammal, comprising administering at least one antigen to the mammal, and further administering at least one amphipathic compound comprising a lipophilic group derived from a sterol linked to a polar

group via a carbamoyl group. Since Bolcsak fails to suggest a carbamoyl linkage, Bolcsak fails to suggest the claimed method. Moreover, since Bolcsak fails to suggest a method of specifically inducing a cytotoxic T cell response or a TH_1-type immune response, Bolcsak fails to suggest the methods of claims 78 and 79.

b. Gao Teaches DNA Transfection, Not a Vaccine or an Adjuvant

Gao provides that 3-β-[N-(N',N'-dimethylaminoethan)-carbamoyl] cholesterol ("DC-Chol") liposomes facilitate DNA mediated transfection in certain types of cells. Gao fails to suggest the claimed invention, because Gao fails to suggest a vaccine composition, and is silent concerning either vaccine compositions and antigens. Therefore, Gao fails to suggest the invention of claims 25-86.

2. Bolcsak and Gao Cannot Properly Be Combined

Teachings of references can be combined *only* if there is some suggestion or incentive to do so. *In re Fine*, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988) (emphasis in original). To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present *evidence*, preferably in the form of some teaching, suggestion, incentive or inference in the applied prior art, or in the form of generally available knowledge, that one having ordinary skill in the art *would have been led* to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention. *Ex parte Levengood*, 28 USPQ2d 1300, 1301 (BPAI 1993) (emphasis in original).

a. There Is Neither Suggestion Nor Motivation To Combine Bolcsak and Gao

The Examiner has identified *no* suggestion in the prior art of the desirability of combining Bolcsak and Gao. Indeed, Bolcsak is devoid of *any* suggestion of an amphipathic compound possessing a lipophilic group derived from a sterol linked to a cationic group via a carbamoyl group. Moreover, Gao is devoid of *any* suggestion to use DC-Chol to make a vaccine. Because there is no objective teaching to combine Bolcsak and Gao, one of ordinary skill in the art would never have been motivated to combine the two documents.

The claimed invention encompasses nucleic acid antigens, protein antigens, and peptide antigens. However, the fact that DC-Chol liposomes purportedly facilitate DNA transfection *in vitro* (Gao) would not have led the artisan to use DC-Chol in a vaccine composition containing a nucleic acid antigen, much less protein or peptide antigens.

The Examiner states:

> It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted the liposome composition taught by Gao et al. in the vaccine preparations taught by Bolcsak et al. in order improve endocytosis, prolong shelf-life, and reduce toxicity of the immunogenic composition, because these characteristics are as desirable for vaccine adjuvants as they are for transfection compositions.

Office Action at 6. Applicants respectfully disagree. The Examiner's proffered basis for combining Bolcsak and Gao is insufficient because it is merely a conclusory statement that is not supported by any objective evidence. The Examiner's proffered basis reflects the incorrect assumption that it would have been reasonable to combine the teachings of Bolcsak and Gao. As discussed above, there is no objective evidence of the desirablity of combining Bolcsak and Gao.

Concerning toxicity, it is true that it is desirable to minimize toxicity. However, for a vaccine adjuvant, such as the amphipathic compound recited in the claims, a "degree of toxicity"

is acceptable, and researchers balance toxicity against adjuvanticity. Gupta, R. K. *et al.*, *Vaccine 11*: 293 (1993) ("Gupta") is of record in the present application as document AT1 on Form PTO-1449. Gupta provides:

> At present the choice of adjuvants for human vaccination reflects a compromise between a requirement for adjuvanticity and an acceptable low level of side effects.

See Gupta at the abstract (last sentence). Gupta further provides:

> It appears that the toxicity can be ascribed in part to the unintended stimulation of various mechanisms of the immune response. Consequently, safety and adjuvanticity must be balanced to get the maximum immune stimulation with minimum side effects.

See Gupta at page 300, the first paragraph of the "Conclusion" section. Thus, for an adjuvant, some degree toxicity can be acceptable if the beneficial degree of adjuvanticity outweighs the degree of toxicity.

One of ordinary skill in the art would *not* have been led by Gao to modify the teachings of Bolcsak in an attempt to obtain the present invention. Gao relates to a cationic liposome reagent that purportedly facilitates the transfection DNA into cells *in vitro*. DNA transfection relies on either endocytosis or cell fusion. Although the mechanism by which a vaccine adjuvant works has not been clearly elucidated, it is believed that neither endocytosis nor cell fusion are considered indispensable. Indeed, Gupta provides:

> They [adjuvants] are also highly variable in terms of how they affect the immune system and in terms of the profile of their side effects. The mode of action of adjuvants was summarized by Chedid[] as : (i) the formation of a depot of antigen at the site of inoculation which is slowly released; (ii) the presentation of antigen to immunocompetent cells; and (iii) the production of different lymphokines such as various interleukins and tumour necrosis factor.

Gupta at 293, right column, last full paragraph (citation omitted).

Thus, while it is possible that the mechanism by which an adjuvant works involves endocytosis or cell fusion, because one of ordinary skill in the art would have known from Gupta that endocytosis or cell fusion are not mechanisms by which an adjuvant was thought to work, one of ordinary skill in the art would not have looked to Gao for guidance concerning an adjuvant.

Moreover, Applicants have discovered that an amphipathic compound possessing a lipophilic group derived from a sterol linked to a cationic group via a carbamoyl group is active as a vaccine adjuvant. In some embodiments of the claimed invention (e.g., claim 33), the amphipathic compound also comprises a neutral lipid. To the extent that Gao discusses a composition containing two lipids, Gao fails to suggest a compound that provides adjuvant activity. Thus, one of ordinary skill in the art would *not* have turned to Gao for guidance concerning an adjuvant.

For the above reasons, one of ordinary skill in the art would never have been motivated to combine Bolcsak and Gao.

b. Only In Hindsight Could The Combination Of Bolcsak and Gao Be Considered, Hypothetically, Desirable

It is only because the teachings of the specification were available that the Examiner was able to search through the prior art in an attempt to find some hypothetical combination of teachings that might suggest the claimed invention. However, only by relying upon Applicants' specification has the Examiner been able to assert, incorrectly, that a *prima facie* case of obviousness exists, and use of such hindsight is impermissible. *See Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 USPQ2d 1434, 1438 (Fed. Cir. 1988); *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1092, 227 USPQ 337, 343 (Fed. Cir. 1985).

Moreover, even if Bolcsak and Gao were hypothetically combined, which cannot properly be done, they would still fail to suggest the claimed invention.

3. Even In Combination, Bolcsak and Gao Fail To Suggest The Claimed Invention

To establish a *prima facie* case of obviousness, the cited documents must suggest *all* of the claim limitations. *See* M.P.E.P. §§ 706.02(j) and 2142; *see also Panduit Corporation v. Dennison Mfg. Co.*, 1 USPQ 2d 1593, 1603 (Fed. Cir. 1987) (A disregard of claim limitations renders claim examination meaningless."); and *In re Lowry*, 32 USPQ 2d 1031 (Fed. Cir. 1994) ("The Patent and Trademark Office must consider all claim limitations when determining patentability of an invention over the prior art."). However, even if Bolcsak and Gao were hypothetically combined, which cannot properly be done, they would still fail to suggest the claimed invention. Even in combination, Bolcsak and Gao fail to suggest the specific amphipathic compounds of claims 32, 45, 57, 73. And 86. Even in combination, Bolcsak and Gao fail to suggest a method of inducing a cytotoxic T cell response as required by claims 64 and 78. Even in combination, Bolcsak and Gao fail to suggest a method of inducing a TH_1-type immune response, as required by claims 65 and 79. Therefore, Bolcsak and Gao fail to suggest the claimed methods.

Even when hypothetically combined, Bolcsak and Gao fail to provide a reasonable expectation of success that DC-Chol would serve as an effective adjuvant in a vaccine composition. Absent a reasonable expectation of success, Bolcsak and Gao cannot render the claimed invention obvious. *See In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); and M.P.E.P. §§ 706.02(j) and 2142.

4. Summary

Bolcsak and Gao fail to suggest the claimed invention. This rejection is improper, and Applicants respectfully request that it be reconsidered and withdrawn.

B. Popescu and Epand Fail To Establish A Prima Facie Case of Obviousness

1. Popescu and Epand Each Fail To Suggest the Claimed Invention

a. Popescu Fails to Suggest a Carbamoyl Linkage

Claims 25-37 are directed to a vaccine composition comprising at least one antigen and at least one amphipathic compound possessing a lipophilic group derived from a sterol linked to a cationic group via a carbamoyl group. Popescu provides liposomes formed from dimyristolyphosphatidylcholine (DMPC)/cholesterol liposomes and an antigen. Popescu fails to teach an amphipathic compound possessing a lipophilic group derived from a sterol linked to a cationic group via a carbamoyl group. Therefore, Popescu fails to teach the invention of claims 25-37.

Claims 30-32 recite specific amphipathic compounds. Because Popescu fails to suggest any of the recited compounds, Popescu fails to suggest the invention of claims 30-32.

Claim 35 requires that the vaccine composition also contain one of two specific neutral lipids. Because Popescu fails to suggest a composition containing both an amphipathic compound (with a carbamoyl linkage) and a neutral lipid, Popescu fails to suggest the invention of claim 35.

Claims 38-49 are directed to a method of making the vaccine composition of claim 25. For the same reasons that Popescu fails to suggest the invention of claim 25, Popescu fails to suggest the invention of claims 38-49.

Claims 50-61 are directed to the vaccine composition obtained by the method of claim 38, which in turn depends from claim 25. Because Popescu fails to suggest the invention of claim 25, Popescu fails to suggest the invention of claims 50-61.

Claims 62-73 are directed to methods for inducing an immune response comprising administering the vaccine composition of claim 25 to a mammal. For the same reasons that

Popescu fails to suggest the invention of claims 25, Popescu fails to suggest the invention of claims 62-73. Moreover, since Popescu fails to suggest a method of specifically inducing a cytotoxic T cell response or a TH_1-type immune response, Popescu fails to suggest the methods of claims 64 and 65.

Claim 74 is directed to a product comprising at least one antigen and one amphipathic compound possessing a lipophilic group derived from a sterol linked to a cationic group via a carbamoyl group. Because Popescu fails to suggest a carbamoyl linkage, Popescu fails to suggest the invention of claim 74.

Claims 75-86 are directed to a method for inducing an immune response in a mammal, comprising administering at least one antigen to the mammal, and further administering at least one amphipathic compound comprising a lipophilic group derived from a sterol linked to a polar group via a carbamoyl group. Since Popescu fails to suggest a carbamoyl linkage, Popescu fails to suggest the claimed method. Moreover, since Popescu fails to suggest a method of specifically inducing a cytotoxic T cell response or a TH_1-type immune response, Popescu fails to suggest the methods of claims 78 and 79.

Since Popescu fails to specifically suggest administering a vaccine composition by the either the mucosal or the intranasal routes, Popescu fails to suggest the invention of claims 68, 69, 81 or 82.

b. Epand Teaches DNA Transfection, Not a Vaccine or an Adjuvant

Epand provides a method for facilitating the transfer of nucleic acids into cells using a mixed lipid dispersion of a cationic lipid with a co-lipid in a suitable carrier solvent. Epand provides that the cationic lipid can be cholesteryl-3β-carboxamidoethylenetrimethylammonium

iodide, cholesteryl-3β-carboxamidoethylenamine, cholesteryl-3β-oxysuccinamidoethylene-trimethylammonium iodide, 3β-(N-(N′, N′-dimethylaminoethane)carbamoyl)cholesterol, and 3β-(N-(polyethylenamine)carbamoyl)cholesterol.

Epand fails to suggest a vaccine composition. Thus, Epand fails to suggest a vaccine composition comprising at least one antigen and at least one amphipathic compound possessing a lipophilic group derived from a sterol linked to a cationic group via a carbamoyl group. Moreover, Epand is silent concerning either vaccine compositions and antigens, and fails to suggest a method of inducing an immune response. Therefore, Epand fails to suggest the invention of claims 25-86.

2. Popescu and Epand Cannot Properly Be Combined

Teachings of references can be combined *only* if there is some suggestion or incentive to do so. To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present *evidence* that one having ordinary skill in the art *would have been led* to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention.

a. There Is Neither Suggestion Nor Motivation To Combine Popescu and Epand

The Examiner has identified *no* suggestion in the prior art of the desirability of combining Popescu and Epand. Indeed, Popescu is devoid of *any* suggestion of an amphipathic compound possessing a lipophilic group derived from a sterol linked to a cationic group via a carbamoyl group. Moreover, Epand is devoid of *any* suggestion to use the disclosed lipids in a vaccine composition. Because there is no objective teaching to combine Popescu and Epand, one of ordinary skill in the art would never have been motivated to combine the two documents.

The claimed invention encompasses nucleic acid antigens, protein antigens, and peptide antigens. However, the fact that certain cationic lipids purportedly facilitate DNA transfection *in vitro* would not have led the artisan to use cationic lipids in a vaccine composition containing a nucleic acid antigen, much less protein or peptide antigens.

Moreover, to the extent that Epand discusses using a neutral lipid with a cationic lipid, Epand fails to provide a reasonable expectation of success that using any neutral lipid would be useful in a vaccine composition, or would induce an immune response. Indeed, the prior art teaches away from that notion. Zhou, X. and L. Huang, *Biochim. Biophys. Acta 1190*: 195-203 (1994) ("Zhou") is of record in the present application as Form PTO-1449 document AR2. Zhou teaches that in complex of DNA and lipopoly(L-lysine) and a co-lipid, substituting DOPC for DOPE as the co-lipid resulted in severely decreased transfection efficiency. Therefore, Popescu and Epand clearly fail to suggest the invention of claims 33-35 and 58-60.

The Examiner states:

> It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the mixed-lipid composition taught by Epand et al. in the vaccine composition of Popescu et al. for an improved adjuvant which would enhance the immune response of the target cells to the immunizing antigen by facilitating cell surface and antigen/lipid interaction.

Office Action at 7. Applicants respectfully disagree. The Examiner's proffered basis for combining Popescu and Epand is insufficient because it is merely a conclusory statement that is not supported by any objective evidence. The Examiner's proffered basis reflects the incorrect assumption that it would have been reasonable to combine the teachings of Popescu and Epand. As discussed above, there is no objective evidence of the desirablity of combining Popescu and Epand. Indeed, Popescu and Epand are so insufficient that, absent Applicants' specification, one

of ordinary skill in the art would never have been motivated to modify the teachings of the Popescu and Epand to obtain the claimed invention.

b. Only In Hindsight Could The Combination Of Popescu and Epand Be Considered, Hypothetically, Desirable

It is only because the teachings of the specification were available that the Examiner was able to search through the prior art in an attempt to find some combination of teachings that might suggest the claimed invention. However, only by relying upon Applicants' specification has the Examiner been able to assert, incorrectly, that a *prima facie* case of obviousness exists, and use of such hindsight is impermissible.

Moreover, even if Popescu and Epand were combined, which cannot properly be done, they would still fail to suggest the claimed invention.

3. Even In Combination, Popescu and Epand Fail To Suggest The Claimed Invention

Even when hypothetically combined, Popescu and Epand fail to suggest the claimed invention. To establish a *prima facie* case of obviousness, the cited documents must suggest *all* of the claim limitations. However, even if Popescu and Epand were hypothetically combined, which cannot properly be done, they would still fail to suggest the claimed invention.

Even in combination, Popescu and Epand fail to suggest a method of inducing a cytotoxic T cell response as required by claims 64 and 78. Even in combination, Popescu and Epand fail to suggest a method of inducing a TH_1-type immune response, as required by claims 65 and 79. Therefore, Popescu and Epand fail to suggest the claimed methods. Even in combination, Popescu

and Epand fail to suggest administering a vaccine composition by either the mucosal or the intranasal routes, as required by claims 68, 69, 81 or 82.

Moreover, even when hypothetically combined, Popescu and Epand fail to suggest the claimed invention, because Popescu and Epand fail to provide a reasonable expectation of success that the cationic lipids taught by Epand would serve as an effective adjuvant in a vaccine composition. Absent a reasonable expectation of success, Popescu and Epand cannot render the claimed invention obvious. *See In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); and M.P.E.P. §§ 706.02(j) and 2142.

4. Summary

Popescu and Epand fail to suggest the claimed invention. This rejection is improper, and Applicants respectfully request that it be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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